Membrane Probes and Sensors for In Vivo Monitoring of Interstitial Fluid Chemicals

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Microdialysis and ultrafiltration probes provide access to individual tissues for in vivo sampling of the interstitial environment. Microdialysis and ultrafiltration are complementary sampling techniques, both utilizing hollow-fiber semi-permeable membrane probes. The membranes are connected to non-permeable micro-bore tubing which provides the fluid connection to the exterior. In microdialysis, fluid is pumped through the membrane and transfer across the membrane is concentration gradient driven. With ultrafiltration, a negative pressure is applied to the membrane and the driving force is a pressure differential. The advantages of these techniques are that they provide methods of sampling from different tissues over long periods of time so that changes due to disease processes or the effects of treatment can be monitored.

Samples obtained from these probes contain only chemicals with molecular weights below the molecular weight cut off of the membrane. With no cellular material present, the samples can usually be analyzed directly with no sample clean-up necessary. In addition to traditional sample analysis methods, there is also the potential of coupling the probes with on-line sensors for real-time monitoring of interstitial changes.

Optimized microdialysis and ultrafiltration probes have been developed to study a number of physiological changes resulting from microgravity. Using the rodent head-down tilt model, electrolyte shifts have been monitored during control periods, head-down tilt, and recovery. Glucose and lactate were also monitored. Work was also done to develop on-line glucose and lactate sensors to be coupled with the microdialysis probes.

Membrane probes have also been developed to investigate changes in skeletal and muscular interstitial chemistry. It has been found that under baseline conditions muscle ultrafilterable calcium (3.50 ± 0.09 mg/dL) is significantly higher ($p < .05$) than bone (2.97 ± 0.20) or subcutaneous tissue (3.21 ± 0.10). However, there were no significant differences in ionized calcium concentrations between these tissues. For magnesium, the bone concentrations are significantly higher than muscle and subcutaneous tissue. The differences between calcium and magnesium distributions indicate that there are differences in homeostatic mechanisms for these two ions. Use of membrane probes permits the tracking of the time course of changes in different tissues after a perturbation. Intravenous infusion of calcium resulted in non-uniform distribution among the tissues studied. Levels rose most rapidly and to the highest level in muscle. Elevations in bone calcium occurred more slowly and did not reach as high a level as in other tissues. These probes have also been used to determine the effect of different dietary calcium levels on interstitial calcium. Twelve sheep were fed 150, 2000, and 15,000 ppm calcium diets. Significant differences were found in the bone, muscle and subcutaneous tissue between diets. Work has also been done to couple on-line calcium sensors with microdialysis probes to develop a system for automated real-time monitoring.

These techniques have potential for broad application, both in physiological and pharmacological research. They can be used to study drug distribution and pharmacokinetics as well as resulting changes in interstitial fluid chemistry. Potential uses include the study the distribution of antineoplastic drugs to tumors and healthy tissue and differences in response to drugs between tumors and normal tissue. In addition to sampling, microdialysis probes provide an access into specific tissues for localized introduction of drugs. While some work has been done using microdialysis probes as a method of delivery, the full potential of this application has not yet been investigated.